

We claim:

1. An isolated human monoclonal antibody, or an antigen binding portion thereof,
that specifically binds to HER2/neu, wherein the antibody or antigen binding portion
5 thereof has one or more of the following characteristics:
 - a) a binding affinity constant to HER2/neu of at least about 10^7 M^{-1} ;
 - b) the ability to opsonize a cell expressing HER2/neu;
 - c) the ability to inhibit growth or to mediate cytolysis of a cell expressing
HER2/neu in the presence of human effector cells at a concentration of about $10 \mu\text{g/ml}$
10 or less *in vitro*; or
 - d) the ability to be internalized by HER2/neu expressing cells after binding to
HER2/neu.
2. The isolated human antibody of claim 1, or an antigen binding portion thereof,
15 having an isotype selected from the group consisting of IgG1, IgG2, IgG3, IgG4, IgM,
IgA1, IgA2, IgAsec, IgD, and IgE.
3. The isolated human antibody of claim 1, or an antigen binding portion thereof,
which is an IgG1 κ .
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4. The isolated human antibody of claim 1, or an antigen binding portion thereof,
wherein the cell expressing HER2/neu is a tumor cell.
5. The isolated human antibody of claim 4, or an antigen binding portion thereof,
25 wherein the cell expressing HER2/neu is selected from the group consisting of an
adenocarcinoma cell, e.g. salivary gland, stomach and kidney, a mammary gland
carcinoma cell, a lung carcinoma cell, a squamous cell carcinoma cell, and an ovarian
cancer cell.

6. The isolated human antibody of claim 1, or an antigen binding portion thereof, produced by a hybridoma which includes a B cell obtained from a transgenic non-human animal having a genome comprising a human heavy chain transgene and a human light chain transgene fused to an immortalized cell.
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7. The isolated human antibody of claim 1, or an antigen binding portion thereof, produced by a hybridoma selected from the group consisting of 3.F2, 2.E8, 1.D2, 1.B10 and 3.B4, deposited with ATCC® as Accession Number _____.
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8. An isolated human monoclonal antibody, or antigen-binding portion thereof, which mediates cytolysis of cells expressing HER2/neu in the presence of human effector cells.
9. The isolated human antibody of claim 8, or an antigen binding portion thereof,
- 15 which is capable of mediating cytolysis of cells expressing HER2/neu by human effector cells at an IC_{50} of 1×10^{-7} M or less *in vitro*.
10. An isolated human monoclonal antibody, or antigen-binding portion thereof, which inhibits growth of cells expressing HER2/neu.
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11. The isolated human antibody of claim 10, or an antigen binding portion thereof, which is capable of inhibiting growth of cells expressing HER2/neu at an IC_{50} of 1×10^{-7} M or less *in vitro*.
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12. A hybridoma comprising a B cell obtained from a transgenic non-human animal having a genome comprising a human heavy chain transgene and a light chain transgene fused to an immortalized cell, wherein the hybridoma produces a detectable amount of a human monoclonal antibody that specifically binds to HER2/neu.

13. The hybridoma of claim 12, wherein the human monoclonal antibody has one or more of the following characteristics:
- a) a binding affinity constant to HER2/neu of at least about 10^7 M⁻¹;
 - b) the ability to opsonize a cell expressing HER2/neu;
 - 5 c) the ability to inhibit growth or to mediate cytolysis of a cell expressing HER2/neu in the presence of human effector cells at a concentration of about 10 µg/ml or less *in vitro*; or
 - d) the ability to be internalized by HER2/neu expressing cells after binding to HER2/neu.
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14. The hybridoma of claim 13, selected from the group consisting of 3.F2, 2.E8, 1.D2., 1.B10, and 3.B4, deposited with ATCC® as Accession Number _____.
15. A transgenic non-human animal which expresses a human monoclonal antibody that specifically binds to HER2/neu, wherein the transgenic non-human animal has a genome comprising a human heavy chain transgene and a human light chain transgene.
16. A method of producing a human monoclonal antibody that specifically binds to HER2/neu, comprising:
- 20 immunizing a transgenic non-human animal having a genome comprising a human heavy chain transgene and a human light chain transgene with HER2/neu or a cell expressing HER2/neu, such that antibodies are produced by B cells of the animal;
 - isolating B cells of the animal; and
 - fusing the B cells with myeloma cells to form immortal, hybridoma cells that
 - 25 secrete human monoclonal antibodies specific for HER2/neu.
17. A bispecific molecule comprising a first binding specificity which is a human monoclonal antibody, or an antigen binding portion thereof, that specifically binds to HER2/neu, and a second binding specificity for an Fc receptor.
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18. The bispecific molecule of claim 17, wherein the Fc receptor is a human FcγRI or a human Fcα receptor.

19. The bispecific molecule of claim 17, which binds to the Fc receptor at a site which is distinct from the immunoglobulin binding site of the receptor.
20. The bispecific molecule of claim 17, wherein the second binding specificity
5 which binds to an Fc receptor is a human monoclonal antibody or an antigen binding portion thereof.
21. The bispecific molecule of claim 17 which is a single chain or Fab' fusion protein.
- 10 22. A multispecific molecule comprising a first binding specificity which is a human monoclonal antibody, or an antigen binding portion thereof, that specifically binds to HER2/neu, a second binding specificity for an Fc receptor, and a third binding specificity for a tumor antigen other than HER2/neu.
- 15 23. The multispecific molecule of claim 22, wherein the third binding specificity is EGF.
24. A composition comprising an isolated human monoclonal antibody or antigen-
20 binding portion thereof of claim 1, and a pharmaceutically acceptable carrier.
25. A composition comprising a combination of two or more isolated human antibodies or antigen-binding portions thereof according to claim 1, wherein each of said antibodies or antigen-binding portions thereof binds to a distinct epitope of HER2/neu.
- 25 26. A method of inhibiting growth of a cell expressing HER2/neu, comprising contacting a cell expressing HER2/neu with an isolated human monoclonal antibody, or an antigen binding portion thereof, that specifically binds to HER2/neu, such that the growth of the cell expressing HER2/neu is inhibited.

27. A method of inducing cytolysis of a cell expressing HER2/neu, comprising contacting a cell expressing HER2/neu with an isolated human monoclonal antibody, or an antigen binding portion thereof, that specifically binds to HER2/neu, in the presence of an effector cell, such that cytolysis of the cell expressing HER2/neu occurs.

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28. A method of treating or preventing a disease characterized by aberrant expression of HER2/neu, comprising administering to a subject an isolated human monoclonal antibody, or an antigen binding portion thereof, that specifically binds to HER2/neu in an amount effective to treat or prevent the HER2/neu-mediated disease.

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29. The method of claim 28, wherein the human monoclonal antibody is conjugated to a binding specificity for a Fc receptor.

30. The method of claim 28, wherein the human monoclonal antibody is conjugated to a cytotoxin.

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31. The method of claim 28, wherein the disease is a cancer.

32. The method of claim 31, wherein the cancer is selected from the group consisting of an adenocarcinoma, *e.g.* salivary gland, stomach and kidney, mammary gland carcinoma, lung carcinoma, squamous cell carcinoma, and ovarian cancer.

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33. A method for detecting the presence of HER2/neu antigen, or a cell expressing HER2/neu, in a sample comprising:

25 contacting the sample, and a control sample, with a human monoclonal antibody, or an antigen binding portion thereof which specifically binds to HER2/neu, under conditions that allow for formation of a complex between the antibody or portion thereof and HER2/neu; and

 detecting the formation of a complex,

30 wherein a difference complex formation between the sample compared to the control sample is indicative the presence of HER2/neu in the sample.

34. An expression vector comprising a nucleotide sequence encoding a variable and constant region of the heavy and light chains of a human monoclonal antibody, or an antigen binding portion thereof, that specifically binds to HER2/neu, wherein the antibody or antigen binding portion thereof has one or more of the following
- 5 characteristics:
- a) a binding affinity constant to HER2/neu of at least about 10^7 M^{-1} ;
 - b) the ability to opsonize a cell expressing HER2/neu;
 - c) the ability to inhibit growth or to mediate cytolysis of a cell expressing HER2/neu in the presence of human effector cells at a concentration of about $10 \mu\text{g/ml}$
 - 10 or less *in vitro*; or
 - d) the ability to be internalized by HER2/neu expressing cells after binding to HER2/neu.
35. An expression vector of claim 34, wherein the antibody or an antigen binding
- 15 portion thereof, is produced by a hybridoma selected from the group consisting of 3.F2, 2.E8, 1.D2, 1.B10 and 3.B4, deposited with ATCC® as Accession Number _____.